



# Pulmonary Tuberculosis Coinfected with COVID-19 Compounded by Bacterial Superinfection: A Case Report and Critical Appraisal of The Evidence Regarding Its Mortality

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## Abstract

**Background:** The WHO has declared COVID-19 as a global pandemic. However, Indonesia is also challenged by high burden of tuberculosis (TB). In this study, reported an active pulmonary TB case coinciding with COVID-19 but deceased due to bacterial infection. There is a need to further explore this new problem in developing countries to determine the prognosis of COVID-19 patients with tuberculosis infection.

**Methods:** A comprehensive literature search was conducted by using databases such as The Cochrane Library, PubMed, Google Scholar, EBSCO-Host, and Scopus, including systematic reviews of cohort studies, cohorts, and case controls. As many as 309 studies were identified, after screening for duplicates and against the inclusion and exclusion criteria, three studies were included for critical appraisal.

**Results:** The meta-analysis by Gao et al included two studies with an odds ratio (OR) of 1.4 [95% CI=0.1-18.93], the cohort study by Sy et al reported a relative risk (RR) of 2.17 [95% CI=1.4-3.37], and Motta et al showed that COVID-19 patients with tuberculosis had a mortality rate of 11.8% [95% CI=7.75-15.45].

**Conclusion:** TB has yet to be identified as a major predictor of increased mortality in COVID-19 patients but can be considered a predictor of increased severity in COVID-19 patients. Studies with a bigger sample size and better study design are suggested to obtain new evidence.

**Keywords:** COVID-19, mortality, *Mycobacterium tuberculosis*, SARS-CoV-2, tuberculosis

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## INTRODUCTION

The World Health Organization (WHO) has declared COVID-19 as a global pandemic in 2020. In Indonesia, the prevalence of COVID-19 cases and mortality continue to increase until the end of 2020. COVID-19 is known for several comorbidities that may increase the risk of severity and mortality, including hypertension, diabetes, and tuberculosis. Both tuberculosis and COVID-19 are infectious diseases that affect human respiratory system with similar symptoms, such as cough, fever, and breathing difficulty.<sup>1</sup>

It is suggested that tuberculosis causes a higher risk of mortality in COVID-19 patients. Pulmonary tuberculosis (pulmonary TB) can damage the lung parenchyma and increase the susceptibility of the hosts' immune system. Meanwhile, COVID-19

can also destroy the lungs and impair the patient's immunity by causing a cytokine storm, increasing the possibility of acute distress syndrome and subsequently causing death.<sup>2,3</sup> A meta-analysis exploring the relationship between tuberculosis and the severity and mortality of COVID-19 patients suggested that coinfection with tuberculosis doubled the risk of severity, despite no statistical difference.<sup>2,3</sup> A case of pulmonary TB co-infected with COVID-19 but passed away due to bacterial infection was reported. This study aimed to explore the possible relationship between pulmonary tuberculosis and COVID-19, especially regarding the mortality of patients with COVID-19 and active TB infection.

## CASE

A 42-year-old male was admitted to the

hospital due to high-grade fever, productive cough and difficult breathing for the past five days. The patient was under routine insulin injection for type 2 diabetes mellitus. Physical examination showed lethargic, with a respiratory rate of 36 X/minute, heart rate of 110x/minute, blood pressure 160/90 mmHg, a temperature of 40°C, oxygen saturation of 92% with 6 liters nasal cannula, and BMI of 20. Rales were identified following lung auscultation, mostly on the upper right hemithorax. Six weeks earlier, he was diagnosed as bacteriologically confirmed pulmonary tuberculosis and has been treated with 4FDC (fixed dose combination anti tuberculosis agents) from

primary health center.

Laboratory findings showed a normal hemoglobin level with mild leukocytosis and a high neutrophil-to-lymphocyte ratio (NLR). Marker of inflammation was high (high C-Reactive Protein and high Ferritin) with low procalcitonin and signs of coagulopathy with high D-dimer and fibrinogen and low albumin level. The latest HbA1C level was still high (Table 1). Chest X ray showed infiltration in both side of the lung and cavity on the right lung consistent with pneumonia and tuberculosis (Figure 1A).

Table 1. Laboratory finding of the case

Laboratory finding	Day 1	Day 8	Day 16	Normal values	Unit
Haemoglobin	13.1	10.6	12.6	13.0-16.0	g/dL
Hematocrite	37.5	31.4	33.4	40.0-48.0	%
Erythrocyte	4.50	3.60	4.10	4.50-5.50	10 <sup>6</sup> /uL
Platelets	590.000	236.000	360.000	150-400	10 <sup>3</sup> /uL
Leukocyte	11.82	9.24	19.24	5.00-10.00	10 <sup>3</sup> /uL
Diff count					
Basophile	0.2	0.8	0.4	0-1	%
Eosinophile	1.9	0.0	0.0	1-3	%
Neutrophiles	80.1	85.6	90.6	52.0-76.0	%
Lymphocyte	12.0	6.8	4.9	20-40	%
Monocyte	5.8	6.8	4.8	2-8	%
Neutrophile to Lymphocyte Ratio	6.68	12.59	14.19	-	-
Haemostasis					
APTT	36.4	35	49.3	31.0-47.0	second
Control	34.8	34	34.8		second
Fibrinogen	696	320	433	136-384	mg/dL
D dimer	4360	1050	1200	0-500	ug/L
CK	539	-	-	30-200	U/L
CK MB	26.6	-	-	<25	U/L
hsTroponin I	19.2	-	24	<26	Pg/mL
HbA1C	10.5	-	-	< 5.8	%
Blood glucose	135	-	200	70-200	mg/dL
Immunoserology					
CRP	207.50	160.80	343.90	<=5.0	mg/L
Ferritin	1400.1	-	1700	20.0-250.0	ng/mL
Procalcitonin	0.17	-	3.5	<0.05	ng/mL
HIV	Negative	-	-	<1.0: Non reaktif	
IGG SARS-CoV-2	Positive	-	-	MRR	S/CO
Blood gas analysis					
pH	7.465	7.388	7.255	7.350-7.450	-
pCO <sub>2</sub>	34.60	45.20	64.40	35.00-45.00	mm Hg
pO <sub>2</sub>	67.70	90.50	77.20	75.00-100.00	mm Hg
HCO <sub>3</sub>	25.10	27.40	29.30	21.00-25.00	mmol/L
O <sub>2</sub> saturation	94.50	28.80	92.40	95.00-98.00	%
Standard HCO <sub>3</sub>	26.4	26.9	25.8	22.0-24.00	mmol/L
Lactate	4.2	-	-	-	mmol/L
Blood calcium	4.1	7.4	7.6	8.4-10	mg/dL
Blood magnesium	4.0	2.2	1.5	1.6-2.6	mg/dL
Others					
Albumin	2.80	2.40	2.20	g/dL	3.5-5.2
SGOT/SGPT	27/26	14/40	25/25	U/L	5-34/0-55
Ureum/Creatinin	66/1.3	68	177/2.6	mg/dL	19-44

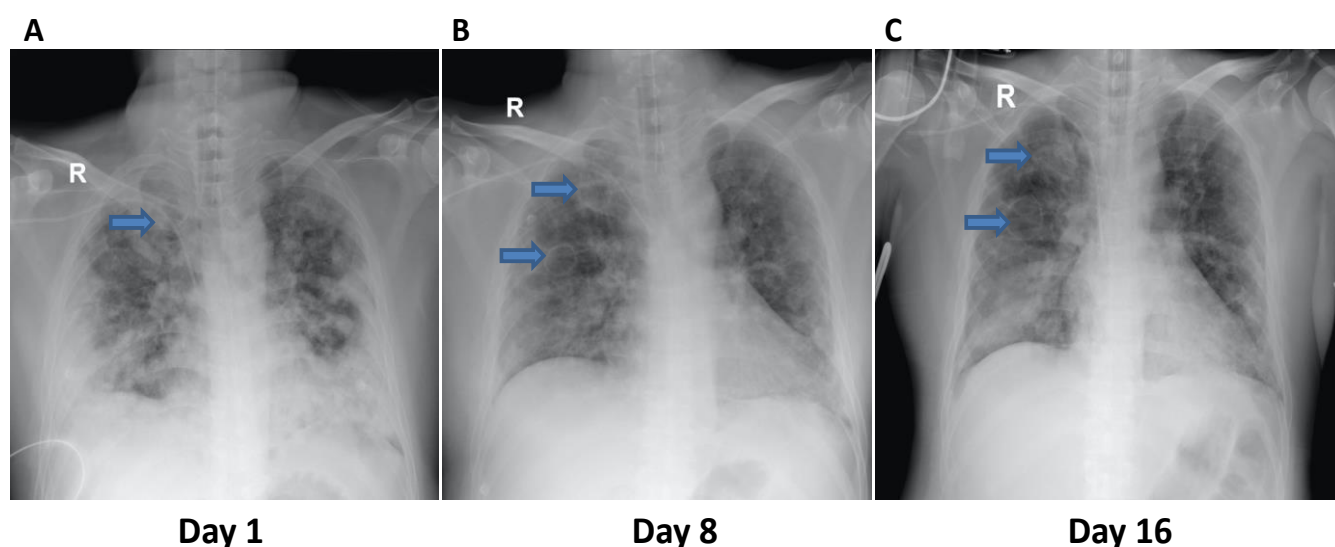


Figure 1. Serial Chest X rays; A) CXR taken on the day 1 showed both fibroinfiltrate, cavity (arrow) and bilateral infiltrate; B) CXR taken on day 8 showed infiltrate improvement but cavities were clearly visible; C) CXR taken on day 16 showed increase infiltrate compare with (B) compatible with pneumonia

Positive result from morning AFB confirmed active TB diagnosis, and repeated SARS-CoV-2 RT-PCR from nasopharyngeal also showed positive result with Ct value of 21. The patient was treated with standard COVID-19 care according to Indonesian National COVID-19 Guideline ie. oxygen therapy with HFNC 70 liter/m,  $\text{FiO}_2=80\%$ ); heparin as an anticoagulant; intravenous corticosteroid, intravenous remdesivir and standard treatment for diabetes mellitus with insulin and antituberculosis drugs in addition to symptomatic treatment and multivitamins.

The patient deteriorated after 12 hour and intubation/mechanical ventilator support was applied and levofloxacin as antibiotic was added. He was clinically and radiologically improved after 7 days in the ICU (Figure 1B) but could not wean from ventilator. SARS-CoV-2 RT-PCR testing on day 7 was still positive, but viral load showed improvement with Ct value  $>30$ .

On day 16, his condition deteriorated with fever, and maximum ventilator setting. Bacterial pneumonia was suspected. Laboratory findings consistent with bacterial infection with increased procalcitonin and high C-reactive protein (Table 1), CXR showed new infiltrate compared to previous CXR on day 8 (Figure 1B and 1C). Culture from endotracheal aspirate and blood showed multidrug resistance *Acinetobacter baumannii* (Table 2).

SARSCOV2 RT PCR testing on day 15 was still positive, but viral load showed improvement with Ct value  $>30$ . Despite appropriate antibiotic and supportive care with mechanical ventilation, the patient passed away on day 20 of hospitalization due to bacterial sepsis.

Table 2. Culture of laboratory finding of the case

Culture	ETT aspirate	Blood
<i>Acinetobacter baumannii</i>	Positive	Positive
Ampicillin /sulbactam	R	R
Pipperacillin tazobactam	R	R
Cefazolin	R	R
Ceftazidime	R	R
Ceftriaxone	R	R
Cefepime	R	R
Meropenem	R	R
Amikacin	R	S
Gentamycin	R	R
Ciprofloxacin	R	R
Tigecycline	S	I
Trim+Sulfamethoxazol	S	R

## DISCUSSION

Based on the Indonesian Ministry of Health data in 2013–2014, the prevalence of positive smear TB in Indonesia was 257 per 100000 population aged  $>15$  years old. In 2017, 420994 new tuberculosis cases occurred in Indonesia.<sup>4</sup> New data from the WHO estimated that total TB incidence was 845000, equivalent to 312/100000 Indonesian population, and with increasing MDR-TB cases, an estimated incidence of 24000 in 2019 in Indonesia.<sup>5</sup>

Indonesia suffered COVID-19 pandemic since its first case was reported in March 2020. By the end of January 2021, more than 1 million COVID-19 cases were reported, with a mortality of more than 30000 deaths. Both tuberculosis and COVID-19 could pose a double burden of infectious diseases, especially in high burden countries such as Indonesia. Observational studies in countries with a high number of BCG vaccines as TB prevention showed fewer COVID-19 cases.<sup>2</sup> Earlier research also showed BCG vaccinations provided immunity and could reduce COVID-19 infection and its progression; however, more evidence is needed to confirm the finding.

A case of pulmonary TB co-infected with COVID-19 but passed away due to bacterial infection was reported. A forty two-years-old male with confirmed pulmonary TB and type 2 diabetes mellitus was admitted to the hospital with acute high-grade fever and dyspnea with severe clinical presentation suggesting COVID-19. CXR showed a cavity and fibro infiltrate consistent with tuberculosis. TB diagnostic standard test or AFB was positive, and SARS-CoV-2 RT-PCR was also positive from nasopharyngeal swabs. The patient slowly recovered after 7 days supported by mechanical

ventilation in the ICU. Unfortunately, the patient infected with Gram Negative bacteria and sepsis was inevitable despite maximal therapy. The patient passed away after 20 days in the ICU.

In high-tuberculosis burden countries, tuberculosis diagnosis should not be overlooked during the COVID-19 pandemic. Recently, Singapore reported four cases of foreign workers presenting with TB and COVID-19 from countries with a high number of tuberculosis cases. Clinical manifestations and atypical radiographic features of COVID-19, such as pleural effusion and cavity, led to the diagnosis of TB through positive interferon-gamma release assay and culture results. All of 4 cases were recovered and continue antituberculosis drugs in outpatient clinic.<sup>6</sup>

Favorable outcome of TB-COVID-19 coinfection was also seen in a referral hospital in Italy of which only 1 patient died among 20 TB-COVID-19 (5% mortality rate).<sup>7</sup> On the contrary, 27.3% mortality rate was reported in India among active/treated TB and COVID-19.<sup>8</sup> The clinical case was a confirmed TB on antituberculosis treatment, coinfecting with COVID-19 but died after severe bacterial infection.<sup>9-11</sup>

Table 3. Critical appraisal of selected studies.

Assessment Indicator	Gao Y et al (2020)	Sy KTL et al (2020)	Mottal I et al (2020)
Validity Assessment of Meta-Analysis Study			
Does the systematic review address a focused question (PICO)?	+	N/A	N/A
.... And use it to direct the search and select articles for inclusion?	+	N/A	N/A
Did the search find all the relevant evidence?	-	N/A	N/A
Have the studies been critically appraised?	+	N/A	N/A
Did they only include high quality studies?	+	N/A	N/A
Have the results been totaled up with appropriate summary tables and plots?	+	N/A	N/A
.... And heterogeneity between studies assessed and explained?	+	N/A	N/A
Validity Assessment of Cohort Study			
Was a defined, representative sample of patients assembled at a standard (usually early) point in the course of their disease?	N/A	+	+
Was patient follow-up sufficiently long and complete	N/A	+	+
Were objective outcome criteria applied in a "blind" fashion?	N/A	-	-
If subgroups with different prognoses are identified, was there adjustment for important prognostic factors?	N/A	-	+
Was there validation in an independent group ("test-set") of patients?	N/A	-	-
Importance Assessment			
How likely are outcomes over time?	OR=1.4	RR=2.17	Risk=11.6%
How precise are the prognostic estimates?	CI=0.1-9.93	CI=1.4-3.37	Unclear

Note: OR=odds ratio; RR=relative risk; CI=confidence interval; + clearly stated (Yes); - not stated (No); ? states unclearly

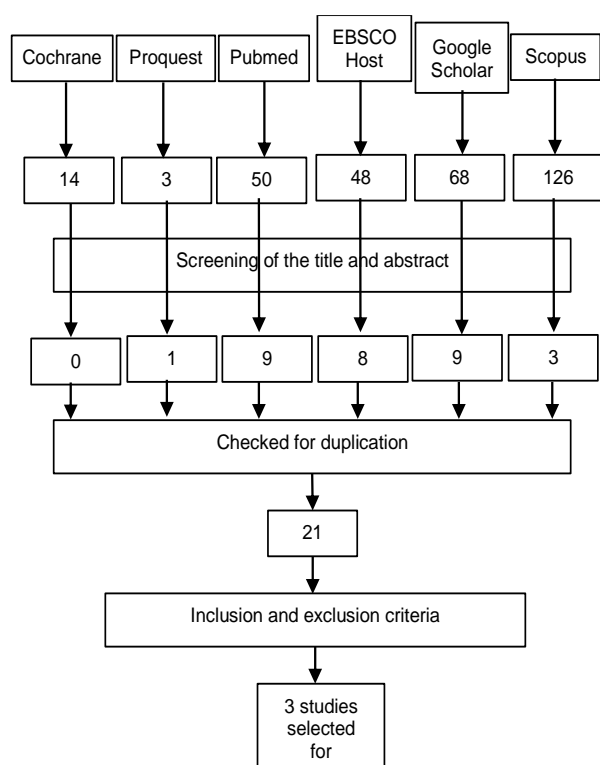


Figure 2. Search strategy regarding mortality among Tuberculosis and COVID-19 coinfections

Note Searching Terminology:

- Pubmed: Search: (("severe acute respiratory syndrome coronavirus 2"[All Fields] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019-nCoV"[All Fields] OR "COVID-19"[All Fields] OR "SARS-CoV-2"[All Fields]) AND ("tuberculosis"[MeSH Terms] OR tuberculosis[Text Word])) AND ("severity" OR "mortality" OR "prognosis")
- Cochrane: "COVID-19" OR "SARS-COV 2" OR "SARS-COV-2 Virus" OR "Novel coronavirus") AND ("tuberculosis" OR "mycobacterium tuberculosis infection" OR "mycobacterium tuberculosis" OR "MTB infection") AND ("prognosis" OR "severity" OR "progression" OR "mortality")
- Scopus: (TITLE-ABS-KEY ("COVID-19" OR "SARS-COV 2" OR "SARS-COV-2 Virus" OR "Novel coronavirus") AND TITLE-ABS-KEY ("tuberculosis" OR "mycobacterium tuberculosis infection" OR "mycobacterium tuberculosis" OR "MTB infection") AND TITLE-ABS-KEY ("prognosis" OR "severity" OR "progression" OR "mortality"))
- Proquest: ti("COVID-19" OR "SARS-COV 2" OR "SARS-COV-2 Virus" OR "Novel coronavirus") AND ti("tuberculosis" ) AND ti("prognosis" OR "severity" OR "progression" OR "mortality")
- EbscoHost: ("Covid-19" AND ("Tuberculosis") AND ("Severity" or ("Death") or (Mortality)
- GoogleScholar: allintitle: COVID 19 and TUBERCULOSIS

Based on the clinical case, an evidence-based appraisal regarding the mortality among tuberculosis patients coinfecting with COVID-19 was conducted. A systematic search of evidence was performed on April 6, 2021, involving six databases, namely Pubmed, The Cochrane Library, Google Scholar, Proquest, Scopus, and EBSCO, by using appropriate keywords that included "SARS-CoV-2" and "Tuberculosis." The search strategy results were

then screened for proper titles and abstracts, followed by the removal of duplicates, which yielded 21 articles. Further screening based on the inclusion and exclusion criteria yielded three selected articles compatible with the clinical questions (Figure 2). One study was a meta-analysis study, and the other two studies were cohort studies.<sup>9-11</sup> The Oxford Centre for Evidence-Based Medicine Levels of Evidence tools were used to appraise these articles, as shown in Table 3.

The meta-analysis by Gao et al has a good validity where the study fulfilled almost all the assessment points.<sup>9</sup> However, the study did not include the keywords with MeSH terms and searched for unpublished studies. In the study, there was a clear PICO following the clinical case, and there were also clearly defined eligibility criteria. The literature search was carried out on more than two databases, such as EMBASE, PubMed, Web of Science, CENTRAL, CBM, CNKI. This study was also assessed by two independent reviewers utilizing the Newcastle-Ottawa Quality Assessment Scale (NOS) to determine the quality of the included literature with a score of 6 by Chen et al and a value of 8 by Du et al. The total number of subjects was 382. This study included a summary table and forest plots in the data presented. The heterogeneity test in this study was also performed well.<sup>9</sup> In terms of importance, the pooled Odds Ratio was 1.40 (95% CI=0.10–18.93), which reported no significant association between tuberculosis and increased risk of mortality.

It is suspected that the inconsistent results may be due to differences in follow-up time (41 days for Chen et al and 45 days for Du et al), differences in the treatment regimen, and the small number of samples analyzed in the studies. The wide confidence interval indicated imprecision of the results, which might be due to the small sample size. The study patients were similar to the patients presented in this case report, where the study was conducted on COVID-19 patients with active tuberculosis infection. This study was considered clinically significant. Overall, the level of evidence in this study classified as 2A.



The study by Motta et al has good validity.<sup>10</sup> The study aimed to describe the characteristics of a cohort of deceased COVID-19 patients with active tuberculosis infection. The Global Tuberculosis Network (GTN) database of large observational projects monitoring adverse reactions to anti-TB drugs in 27 centers in 8 countries identified 69 cases of TB and COVID-19. All consecutive cases with TB diagnosis at present or in the past, besides TB sequelae, were included. All patients had the same zero point, with adjusted inclusion and exclusion criteria to have similar characteristics. Patients were also followed for an appropriate length of time until an outcome was achieved. The highlight of the study was that 8 out of 69 patients (11,6%) died. The study concluded that TB might not be a major determinant of mortality, and mortality was likely to occur in elderly patients with comorbidities such as diabetes and cardiovascular disease.<sup>10</sup> Overall, the level of evidence in this study classified as 2B.

The critical appraisal results for the study of Sy et al showed sufficient validity for the cohort study.<sup>11</sup> However, it should be used with caution. Sy et al analyzed the risk of mortality and recovery time in COVID-19 patients with previous and active tuberculosis based on national COVID-19 surveillance in the Philippines. As many as 106 subjects had previous or active tuberculosis with COVID-19 were propensity score-matched with a 4:1 ratio of COVID-19 confirmed subjects to create a comparable population and reduce confounding factors. All subjects were also followed within the appropriate time frame and analyzed accordingly. In the study, blinding was not carried out or did not have a test-set because the outcome evaluated was only mortality, which must be assessed objectively.<sup>11</sup>

The importance assessment in this study was carried out by comparing the risk of recovery time and mortality of COVID-19 patients who were currently infected or previously infected with tuberculosis against those without any tuberculosis. The calculated relative risk was 2.17 (95% CI=1.4–3.37) from this assessment. That study's limitation was the TB definition, in which previous TB diagnosis and current TB disease were considered confirmed

TB, therefore was unable to distinguish between the independent effects of these two groups separately. That study was conducted in the Philippines which share similar characteristics to Indonesians, such as demographics, socioeconomics, and the suitability of the high number of COVID-19 and tuberculosis diseases.<sup>11</sup> Overall, the level of evidence in this study classified as 2B.

Gao et al also assessed the association between tuberculosis and the severity of COVID-19, which reported an OR value of 2.10 (95% CI=0.61–7.18). Although not statistically significant, tuberculosis was shown to increase the severity of COVID-19. Severe COVID-19 was defined as having acute respiratory distress syndrome (ARDS), requiring mechanical ventilation and admission to the intensive care unit (ICU), or required basic life support. Patients suffering from respiratory diseases, such as pulmonary TB, can cause pulmonary dysfunction, resulting in lower defense against the virus and more likely to develop ARDS.<sup>9</sup>

The Center for Disease Control and Prevention (CDC) warned that tuberculosis patients with a minimum age of 65 and had compromised respiratory systems are at a greater risk of suffering from COVID-19 with severe symptoms.<sup>12,13</sup> Chen et al assessed the impact of active and latent tuberculosis on the severity of COVID-19. A study was conducted on 36 positive SARS-CoV-2 patients (based on RT-PCR results) assigned into groups based on the severity of symptoms to mild/moderate and severe/critical cases. Of the 36 patients, 30 patients had IGRA +ve results, three of which were active TB with severe/critical COVID-19. They indicated that the severe/critical group had a significantly higher percentage of TB coinfection in the mild/moderate group (78% vs. 22%;  $P=0.0049$ ). These data suggested that *Mycobacterium tuberculosis* and SARS-CoV-2 coinfection possibly led to increased severity of COVID-19.<sup>12</sup> That case showed that patient with confirmed tuberculosis could also be infected with SARS-CoV-2 and sepsis with severe clinical symptoms.

The person with tuberculosis with slow response with antituberculosis should be evaluated

further. Immunocompetent patient without comorbidities usually response very well with oral antituberculosis drugs and could be evaluated clinically, bacteriologically and radiologically after 2 weeks treatment.<sup>14</sup> This case showed slow recovery during 6 weeks antituberculosis agents despite good adherence and regular treatment. Factor that may delay treatment response could be impaired immune response.<sup>13,14</sup>

The patient had negative HIV test result, but suffered from diabetes mellitus more than 5 years with uncontrolled status most of the time despite treatment with regular insulin. Diabetes has potential impact since it impairs immune response which leads to higher vulnerability to develop active tuberculosis and also slow response to treatment. Immune impairment might also contribute to high susceptibility to severe COVID-19. The patient was further infected with bacteria that resist to most antibiotics available. Bacterial sepsis is well known for bad prognosis especially in those with comorbidities. The severe systemic infection and sepsis was the main reason of deterioration and death in this case.

The hypothesis of impaired immune response ideally should be validated by using surrogate markers, for example CD4/CD8 T cells. However, due to clinical setting and feasibility, the assays could not be performed.

Patient's uncontrolled diabetes mellitus might be the underlying factor which aggravates his overall condition and consistent with a study in Italy by Motta et al<sup>10</sup> and study in India by Gupta et al that claimed that those who died with COVID-19 and tuberculosis had Diabetes Mellitus as comorbid.<sup>8</sup> Secondary bacterial infection might further impair the disease and unfortunate grave prognosis in this case report. Based on metanalysis by Langford et al, secondary bacterial infection was found in 14.3 % of hospitalized COVID-19 patients, and more common in critically ill patient. Most of them had poor prognosis.<sup>15</sup>

Given the increasing number of COVID-19 cases in developing countries, tuberculosis and pneumonia remains a significant health problem in

Indonesia. Effective prevention strategies for tuberculosis and bacterial infection are imperative. Early screening for COVID-19 and bacterial infection in tuberculosis patients with comorbidities, education and monitoring of high-risk patients, and proper comorbid management could help prevent patients' deterioration with a coinfection of tuberculosis, COVID-19 and sepsis.

## LIMITATION

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## CONCLUSION

This case report highlights the possible multi organism infection due to *Mycobacterium tuberculosis*, SARS-CoV-2 virus and aggravated by severe secondary pan-resistant bacterial infection in an individual with comorbid that further worsened the prognosis. Based on this case report, tuberculosis patients are not immune to COVID-19 coinfection. Other comorbidities might play a role in COVID-19 coinfection susceptibilities and disease progression. Based on the current critical appraisal of evidence, tuberculosis is not a major predictor of mortality in patients with COVID-19. However, it can be considered a risk factor for increased severity in COVID-19 patients. There is no enough evidence to answer this question, and better research methodologies such as more suitable study designs and large numbers of subjects are suggested.

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## CONFLICT OF INTEREST

None.

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